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Risk of Monoclonal Gammopathy of Undetermined Significance: A Case-Referent Study

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A retrospective study was conducted in 285 cases of monoclonal gammopathy of undetermined significance (MGUS) and in 570 sex- and age-matched hospital controls in order to investigate the possible association between socioeconomic status, residence, alcohol and tobacco habits, occupation, occupational exposure to toxic substances, chronic antigenic stimulation, and risk of MGUS. Significant associations with the risk of MGUS were found for farmers ($P < 0.005$) and for workers in industry ($P < 0.025$). Occupational exposure to asbestos, fertilizers, mineral oils and petroleum, paints and related products, pesticides, and radiation was significantly ($P < 0.05$) associated with an increase in risk of MGUS. Chronic immune-stimulating conditions, when considered as a group, presented a significant ($P < 0.025$) association with the risk of MGUS, but no specific disease has been found to be significantly associated. These data are in agreement with the previous reports on multiple myeloma, suggesting that these factors may play an important role in the development of monoclonal gammopathies. However, these findings need to be confirmed in prospective larger population-based studies. © 1996 Wiley-Liss, Inc.

Key words: monoclonal gammopathy of undetermined significance, epidemiology, case-referent study, occupation, occupational exposure, antigenic stimulation

INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is characterized by the presence of a monoclonal component in patients without evidence of myeloma, macroglobulinemia or other related diseases [1]. The prevalence of MGUS is considerable, estimated at 1–11% in the adult healthy population [1,2]; in spite of this relatively high frequency, little is known about etiological determinants [1,2]; certain data suggest that some genetic, environmental, occupational, and immunological, such as chronic antigenic stimulation and T-lymphocyte deficiency factors may be responsible of the development of MGUS or overt myeloma [1,2].

The aim of the study was to investigate the possible associations between socioeconomic status, residence, habits, occupation, occupational exposure to toxic substances, and chronic antigenic stimulation, and the risk of MGUS.

PATIENTS, CONTROLS, AND METHODS

A total of 285 cases of MGUS, 173 males (60.7%) and 112 females (39.3%), with an age range of 40–89 years, were considered for the study. The diagnosis of MGUS [1] was based on a serum monoclonal component <30 g/L, plasma cells <10% in bone marrow aspirate, no or <1 g/24 hr amount of Bence Jones proteinuria, absence of anemia, hypercalcemia, bone lytic lesions, and renal failure. The serum monoclonal component was IgG in 216 (75.8%) cases, IgA in 40 (14.0%), and IgM in 29 (10.2%); type κ in 192 (64.4%), and λ in 93 (32.6%); a

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TABLE I. Association Between Socioeconomic Status, Residence, Habits, Occupation, Occupational Exposure, and Chronic Immune-Stimulating Conditions, and Risk of Monoclonal Gammopathy of Undetermined Significance

Categories of risk	Cases (%)	Controls (%)	b/c[a]	OR (95%CI)	χ^2	*P*	EF,%
Socioeconomic status							
High	86 (30.2)	195 (34.2)	22/58	0.76 (0.56 + 1.33)	1.40	ns	—
Medium	109 (38.2)	220 (38.6)	37/87	0.83 (0.62 + 1.61)	0.05	ns	—
Low	90 (31.6)	155 (27.2)	33/41	1.61 (1.18 + 2.19)	1.58	ns	37.9
Residence							
Urban	156 (54.7)	306 (53.7)	43/98	0.88 (0.66 + 1.17)	0.05	ns	—
Rural	129 (45.3)	264 (46.3)	48/85	1.13 (0.85 + 1.50)	0.15	ns	10.7
Habits							
Alcohol intake	105 (36.8)	186 (32.6)	36/65	1.11 (0.86 + 1.44)	0.13	ns	9.9
Tobacco smoke	93 (32.6)	198 (34.7)	44/63	1.40 (1.03 + 1.89)	0.47	ns	—
Occupations							
Private practitioners	28 (9.8)	66 (11.6)	21/58	0.72 (0.43 + 1.21)	1.78	ns	—
Office workers	41 (14.4)	87 (15.3)	29/59	0.98 (0.66 + 1.46)	0.11	ns	—
Teachers	8 (2.8)	18 (3.1)	7/16	0.88 (0.43 + 1.80)	0.08	ns	—
Medical doctors or nurses	9 (3.2)	20 (3.5)	8/19	0.84 (0.38 + 1.87)	0.07	ns	—
Sales workers	6 (2.1)	18 (3.1)	4/16	0.50 (0.20 + 1.27)	0.77	ns	—
Building workers	23 (8.1)	53 (9.3)	18/45	0.80 (0.48 + 1.33)	0.35	ns	—
Industry workers	52 (18.2)	85 (14.9)	27/21	2.57 (1.73 + 3.81)	6.15	<0.025	61.1
Handcraftsmen	16 (5.6)	35 (6.1)	12/27	0.89 (0.48 + 1.64)	0.09	ns	—
Auto mechanics	4 (1.4)	2 (0.4)	4/2	4.00 (1.31 + 12.24)	1.71	ns	75.0
Railroad workers	5 (1.7)	8 (1.4)	4/7	1.14 (0.37 + 3.51)	0.16	ns	12.3
Farmers	70 (24.6)	120 (21.1)	42/34	2.47 (1.74 + 3.51)	10.05	<0.005	59.5
Housekeepers	12 (4.2)	30 (5.3)	8/26	0.62 (0.31 + 1.23)	0.45	ns	—
Others	11 (3.9)	28 (4.9)	8/21	0.76 (0.37 + 1.55)	0.48	ns	—
Exposure							
Acids	34 (11.9)	65 (11.4)	18/33	1.09 (0.70 + 1.79)	0.05	ns	8.3
Aldehydes and ketones	22 (7.7)	46 (8.1)	12/26	0.92 (0.54 + 1.56)	0.03	ns	—
Aliphatic hydrocarbons	28 (9.8)	59 (10.4)	17/35	0.97 (0.60 + 1.56)	0.06	ns	—
Alkalies	51 (17.9)	86 (15.1)	21/46	0.91 (0.62 + 1.33)	1.11	ns	—
Aromatic hydrocarbons	19 (6.7)	24 (4.2)	15/19	1.58 (0.82 + 2.73)	2.40	ns	36.7
Asbestos	20 (7.0)	13 (2.3)	20/13	3.08 (1.51 + 6.29)	11.49	<0.001	67.5
Carbon monoxide	48 (16.8)	78 (13.7)	28/44	1.27 (0.86 + 1.88)	1.51	ns	21.3
Chemical asphyxiants	9 (3.2)	25 (4.4)	6/18	0.67 (0.31 + 1.46)	0.75	ns	—
Chlorinated hydrocarbons	18 (6.3)	38 (6.7)	12/28	0.86 (0.48 + 1.54)	0.04	ns	—
Dusts	68 (23.9)	145 (25.4)	25/66	0.76 (0.55 + 1.06)	0.06	ns	—
Dyes and inks	21 (7.4)	47 (8.2)	16/42	0.76 (0.45 + 1.30)	0.44	ns	—
Esters	11 (3.9)	18 (3.2)	10/17	1.18 (0.55 + 2.53)	0.29	ns	15.3
Ethers	20 (7.0)	41 (7.2)	15/35	0.86 (0.49 + 1.50)	0.01	ns	—
Fertilizers	83 (29.1)	106 (18.6)	40/51	1.57 (1.13 + 2.18)	12.23	<0.0005	36.3
Metals	51 (17.9)	102 (17.9)	26/55	0.95 (0.66 + 1.38)	0.00	ns	—
Mineral oils and petroleum	43 (15.1)	53 (9.3)	24/22	2.18 (1.42 + 3.35)	6.41	<0.025	54.1
Organically high polymers	19 (6.7)	33 (5.8)	16/29	1.10 (0.61 + 1.97)	0.26	ns	9.1
Other caustic substances	11 (3.9)	19 (3.3)	10/16	1.25 (0.56 + 2.78)	0.32	ns	20.0
Paints and related products	35 (12.3)	40 (7.0)	33/36	1.83 (1.13 + 2.95)	6.58	<0.025	45.4
Pesticides	79 (27.7)	108 (18.9)	43/52	1.65 (1.18 + 2.30)	8.56	<0.005	39.4
Radiations	13 (4.6)	4 (0.7)	13/4	6.50 (2.10 + 20.12)	14.52	<0.0001	84.6
Chronic immune-stimulating conditions							
All conditions	178 (62.5)	309 (54.2)	68/89	1.47 (1.09 + 1.97)	5.27	<0.025	32.0
Allergies	8 (2.8)	17 (3.0)	7/15	0.93 (0.40 + 2.18)	0.17	ns	—
Chronic bronchitis	24 (8.4)	44 (7.7)	15/25	1.20 (0.71 + 2.02)	0.13	ns	—
Chronic hepatitis	19 (6.7)	35 (6.2)	14/27	1.04 (0.58 + 1.85)	0.09	ns	—
Collagen-vascular diseases	11 (3.9)	19 (3.2)	10/17	1.11 (0.52 + 2.37)	0.16	ns	9.9
Frequent infections	33 (11.5)	58 (10.2)	26/55	0.94 (0.60 + 1.48)	0.39	ns	—
Glomerulonephritis	6 (2.1)	10 (1.8)	6/10	1.20 (0.43 + 2.34)	0.13	ns	16.7
Inflammatory bowel disease	5 (1.8)	9 (5.9)	5/9	1.11 (0.84 + 2.47)	0.04	ns	9.9
Peptic ulcer disease	31 (10.9)	55 (9.6)	27/49	1.10 (0.69 + 1.75)	0.32	ns	9.1
Prostatitis	3 (1.0)	3 (0.5)	3/3	2.00 (0.40 + 9.98)	0.75	ns	50.0
Pyelonephritis	8 (2.8)	11 (1.9)	7/9	1.56 (0.64 + 3.81)	0.67	ns	35.9
Skin disease	5 (1.8)	8 (1.4)	5/8	1.25 (0.41 + 3.86)	0.16	ns	20.0
Thyroiditis	6 (2.1)	8 (1.4)	5/7	1.43 (0.49 + 4.16)	0.58	ns	30.1
Urinary tract infections	19 (6.3)	32 (5.6)	16/28	1.14 (0.63 + 2.05)	0.38	ns	12.3

[a]Discordant pairs: OR, Mantel–Haenszel odds ratio; 95%CI, confidence intervals at 95% of probability; EF, etiological fraction.

urinary monoclonal component was present in 34 (11.9%) patients, 23 type κ and 11 type λ.

Two controls for each case were matched for sex, age (within 5 years) and hospital. They were selected from the same geographic area as the MGUS cases and from daily inpatient admission registries. Patients with either cancer or congenital disorders were excluded from the study.

All subjects, both cases and controls, were interviewed, without knowledge of the subject's state, socioeconomic status, area of residence (urban or rural), alcohol intake (<100 or >100 mg/day), tobacco smoking, current or previous occupation, exposure to one or more of a list of toxic substances (and whether affected), before admission to hospital, with a pathological condition that could involve a chronic reaction of the immune system. In 196 cases (68.8%) and 509 controls (89.3%), this information was obtained directly; in the other cases, this information was elicited from their relatives and from clinical records.

Exposure to occupational toxic substances was grouped in 21 risk categories, as proposed by Morris et al. [3]. The chronic diseases cited by Isobe and Osserman [4] and by Cohen et al. [5] were considered to stimulate the immune system chronically. A matched-pair analysis was used with the relative risk of MGUS estimated by the odds ratio (OR) of discordant pairs (b/c), and the confidence intervals at 95% of probability (95%CI) were computed on the basis of the normal approximation. The statistical significance of each association was calculated using the Mantel–Haenszel chi-square test corrected for the continuity, with a degree of freedom. Finally, the etiologic fraction (EF) of each association was calculated [6].

RESULTS

Table I summarizes the results. No significant ($P > 0.05$) association was found for socioeconomic status, residence, and habits. Among the cases, a significant excess of workers in industry ($P < 0.025$) and in agriculture ($P < 0.005$) was demonstrated. Occupational exposure to asbestos ($P < 0.001$), fertilizers ($P < 0.0005$), mineral oils and petroleum ($P < 0.025$), paints and related products ($P < 0.025$), pesticides ($P < 0.005$), and radiation ($P < 0.0001$) was significantly associated with the risk of MGUS. The overall OR of chronic antigenic stimulation of cases versus controls was 1.47, with a significant ($P < 0.025$) risk association with MGUS; no specific condition was found to be significantly ($P > 0.05$) associated.

DISCUSSION

This study adds MGUS to our previous observations on the risk of hematological malignancies [7], and multiple myeloma [8]. Whereas several studies investigated the role of occupational exposure [1,2,4,8,9], and of chronic antigenic stimulation [1,2,5,10] in multiple myeloma, using the case-control method, this is the first study to consider these risk factors in MGUS. Despite the limitations of case-control studies [6], the observation of significant associations with some occupational exposure and with overall chronic antigenic stimulation suggests that these factors may play an important role in inducing MGUS. It is worth noting that the same associations have been reported for myeloma [2,4,8,9], and for other lymphoid neoplasms [7], suggesting that the same causes could be involved in the activation of B cells. In effect, MGUS could be considered a preneoplastic condition, as long-term studies show that about 20% of patients develop a malignant plasma cell dyscrasia [1]. It is hypothesized that malignant plasma cell diseases develop through three phases [2]: a polyclonal phase or pre-MGUS, a monoclonal phase or MGUS, and a malignant phase. It is possible that exposure to toxic substances—such as asbestos, which causes a defect in cellular immunity and hyperreactivity in humoral immunity [7–9]; to radiation, actually the only certain environmental factors capable of inducing cancer in humans [2,7–9]; to pesticides and fertilizers, largely employed in agriculture [2,8]; to mineral oils, which injected into the peritoneal cavity of BALB/c mice is the experimental model for monoclonal gammopathies [1,2]; to paints, which contain several potential carcinogens [8]; and to chronic antigenic stimulation [5,9,10]—may induce MGUS, initiating the polyclonal phase or facilitating the passage from a polyclonal to a monoclonal phase. Even if some studies [5,9,10] failed to find a significant association with chronic antigenic stimulation, it is postulated that this condition, with concomitant impairment of T-cell activity and lack of suppression of B cells by T cells, leads to a spontaneous or environmental-induced mutation resulting in monoclonal proliferation of a B-cell clone [1].

In conclusion, some occupational exposure and overall chronic antigenic stimulation seems to enhance the risk of MGUS. Further attention might be paid in particular to these conditions in epidemiological studies, and further larger, prospective, population-based researches appear warranted to assess the strength of any positive association.

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